

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁴ : C07D 401/04, A61K 31/445</p>		<p>A1</p>	<p>(11) International Publication Number: WO 85/03707 (43) International Publication Date: 29 August 1985 (29.08.85)</p>
<p>(21) International Application Number: PCT/US85/00187 (22) International Filing Date: 8 February 1985 (08.02.85) (31) Priority Application Number: 580,304 (32) Priority Date: 15 February 1984 (15.02.84) (33) Priority Country: US</p>		<p>(81) Designated States: AU, DK, FI, HU, JP. Published <i>With international search report.</i></p>	
<p>(71) Applicant: SCHERING CORPORATION [US/US]; Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventor: VILLANI, Frank, J. ; 22 Oakland Terrace, Fairfield, NJ 07006 (US). (74) Agents: MUGFORD, David, J. et al.; Schering-Plough Corporation, One Giralda Farms, Madison, NJ 07940 (US).</p>			
<p>(54) Title: 8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE AND ITS SALTS, PROCESSES FOR THE PRODUCTION THEREOF AND PHARMACEUTICAL COM- POSITIONS CONTAINING THESE COMPOUNDS</p>			
<p>(57) Abstract</p> <p>The compound, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, and the pharmaceutically acceptable salts thereof possess antihistaminic properties with substantially no sedative properties. Methods for preparing and using the compound and salts are described.</p>			

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austria	GA Gabon	MR Mauritania
AU Australia	GB United Kingdom	MW Malawi
BB Barbados	HU Hungary	NL Netherlands
BE Belgium	IT Italy	NO Norway
BG Bulgaria	JP Japan	RO Romania
BR Brazil	KP Democratic People's Republic of Korea	SD Sudan
CF Central African Republic	KR Republic of Korea	SE Sweden
CG Congo	LI Liechtenstein	SN Senegal
CH Switzerland	LK Sri Lanka	SU Soviet Union
CM Cameroon	LU Luxembourg	TD Chad
DE Germany, Federal Republic of	MC Monaco	TG Togo
DK Denmark	MG Madagascar	US United States of America
FI Finland	ML Mali	
FR France		

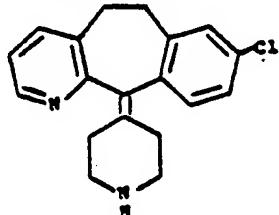
8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE AND ITS SALTS,
PROCESSES FOR THE PRODUCTION THEREOF AND
PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS

BACKGROUND OF THE INVENTION

United States Patent Numbers 3,326,924 and 4,282,233 describe 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines.

SUMMARY OF THE INVENTION

The invention sought to be patented in its chemical compound aspect is 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine having the structural formula:



and the pharmaceutically acceptable salts thereof.

The invention sought to be patented in its pharmaceutical composition aspect is a composition which comprises 8-chloro-6,11-dihydro-11-(4-

-2-

piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

The invention sought to be patented in its pharmaceutical method aspect is a method for treating allergic reactions in a mammal which method comprises administering the above defined pharmaceutical composition to said mammal.

DESCRIPTION OF THE INVENTION

The compound of the invention may be prepared by the decarbethoxylation of 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, which compound may be prepared as described in U.S. patent 4,282,233. Other methods for preparing the compound of the present invention are also contemplated.

For example, 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine may be demethylated to produce the compound of the invention. The 8-chloro-11-(1-methyl-4-piperidylidene) compound may be prepared by methods described in U.S. patent 3,326,924.

The compound of the invention, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine can form salts with pharmaceutically acceptable acids such as hydrochloric, methanesulfonic, sulfuric, acetic, maleic, fumaric, phosphoric and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base form may be regenerated by treating the salt forms with a base. For example, dilute aqueous base solutions may be

-3-

utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base form differs from the respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but the salts are otherwise equivalent to the respective free base form for purposes of the invention.

The compound of the invention and its corresponding salts can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 5 to about 20 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin,

-4-

starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl-cellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxy-methylcellulose and other well-known suspending agents.

-5-

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

Transdermal dosage forms are also contemplated.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate

-6-

quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet or tablet itself or it can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 1000 mg according to the particular application. The compositions can, if desired, also contain other therapeutic agents.

The dosages may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The compound of the invention, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine, possesses anti-histaminic properties. The antihistaminic properties of this compound may be demonstrated by use of standard pharmacological testing procedures. For example, the ability of the compound to reduce histamine-induced paw edema in mice may be measured by use of the following method.

Male CF₁ mice, 25-30 g, are housed under conditions of controlled temperature and humidity with

-7-

a 12 hour dark/light cycle. Food and water are allowed ad libitum. The mice are randomly assigned to the treatment groups. One hour after treatment with compound or vehicle, the mice are lightly anesthetized with ether. The left hind paw of each mouse serves as a control and is injected with 25 μ l of isotonic saline. The right hind paw serves as the experimental paw and is injected with 25 μ l of isotonic saline containing 13 μ g histamine dihydrochloride. Thirty minutes later the mice are killed by cervical dislocation and both hind paws of each mouse are removed by cutting at the tarsal joint. The weight of each paw is recorded and the difference in weight between the compound-treated and the placebo-treated groups is evaluated using Student's "t" test. The ED₅₀ values (the dose causing 50% inhibition of histamine-induced edema) and 95% confidence limits are determined by the Linear Least Square Dose-Response method [Brownlee, K.A., "Statistical Theory And Methodology In Science and Engineering", 2nd Ed., J. Wiley and Sons, New York, 1965, pp. 346-349].

Utilizing this method, the following results were obtained:

<u>Treatment</u>	<u>Oral Dose mg/kg</u>	<u>No. of Animals</u>	<u>Increased Paw</u>	
			<u>Weight (mg)</u>	<u>%Inhibition</u>
Placebo	—	7	22.3	—
Compound of the invention	0.03	8	19.9	11
	0.1	7	13.0	42
	0.3	8	6.1	73
	1.0	8	2.5	89

-8-

The compound of the invention was also tested to assess its sedative effects, since many clinical antihistamines are known to possess the untoward side effect of causing drowsiness and sedation.

Acute behavioral, neurologic and autonomic effects of the compound of the invention were evaluated in mice by a modification of the method of Irwin [Irwin S., *Drug Screening And Evaluation Of New Drugs In Animals, in Animal And Clinical Pharmacologic Techniques in Drug Evaluation*, Nodine JM and Siegler PE (Eds)., Year Book Medical Publishers Inc., Chicago 1964, pp 36-54]. After oral administration of vehicle or drug, mice (CFI males, 20-24 g) were observed and manipulated to evaluate behavioral, neurologic and autonomic changes. A semi-quantitative scoring scale was used where signs normally present (eg, spontaneous activity, alertness, pupil size) were assigned a "normal" score of 0 and scores of +1, +2 and +3 indicated slight, moderate and marked increases and scores of -1, -2 and -3 indicated slight, moderate and marked decreases from "normality". When a sign occurred that is not normally present (eg, convulsions, tremors), its magnitude was graded on a 1-3 scale. Each treatment group consisted of 6 animals and evaluations were conducted 1 hour after dosing. Additional observations for lethality were made for up to 24 hours after dosing. Incidence is defined as the observation occurring in an animal with a score of 2 or greater according to the scoring method defined above.

-9-

Effects of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-
5H-benzo[5,6]cyclohepta[1,2-b]pyridine on behavior
neurologic function and automatic function in mice

<u>Measurement</u>	<u>MED, mg/kg po^a</u>
Lethality	>300
Reactivity	>300
Decreased motor activity	>300
Decreased muscle tone	>300
Tremors/convulsions	>300
Ataxia	>300
Mydriasis	300
Ptosis	300

^aMinimal effective dose, defined as the lowest dose that produced a score of 2 or greater according to Irwin (supra) in at least 3 of 6 animals tested at each dose.

Oral ED₅₀ of the compound of the invention in the free form : 0.15 mg/kg.

From the above test results, it may be concluded that the compound of the invention would be essentially non-sedating at a clinically useful antihistamic dosage.

The amount and frequency of administration of the compound of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgement of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptom being treated. A typical recommended dosage regimen is oral administration of from 5 to 100 mg/day, preferably 10 to 20 mg/day, in two to four divided doses to achieve relief of the symptoms.

-10-

EXAMPLE I

8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE ACETIC ACID SALT

To 12.g sodium hydroxide in 30 ml ethyl alcohol (70%) add 6 g of 8-chloro-6,11-dihydro-11-(1-ethoxy carbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta [1,2-b]pyridine (prepared as described in U.S. patent 4,282,233) and reflux with stirring for 24 hours. After about the first 6-8 hrs. an additional 30 ml of 70% ethyl alcohol may be added.

Remove about 50% of the solvent by distillation in vacuo. Add a small amount of ice water and acidify with glacial acetic acid.

Extract with chloroform (6-8x), since the product precipitates from the acetic acid solution as a thick emulsion which cannot be filtered.

Concentrate the chloroform extracts to a small volume and precipitate the product with hexane. Crude m.p. 197-200°C.

Recrystallize from benzene-hexane to obtain the product, m.p. 199-200°C. Yield 4.0-4.5 g.

EXAMPLE II

8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

The acetic acid salt prepared as in Example I is dissolved in a minimum amount of water and the solution is made basic with a dilute aqueous solution of potassium carbonate. A pink colored oil separates.

Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151-152°C.

-11-

EXAMPLE III

8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

A. 8-Chloro-6,11-dihydro-11-(1-cyano-4-piperidylidene)-
5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

Dissolve 16.2 g (0.05M) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine (prepared by the methods described in U.S. patent 3,326,924) in 300 ml of dry benzene. To this solution, add slowly under nitrogen a solution of cyanogen bromide (6.4 g) dissolved in 75 ml of benzene. Allow this mixture to stir at room temperature overnight (approx. 20 hrs.).

Filter the solution, and concentrate the filtrate in vacuo to a small volume and precipitate the product by the addition of petroleum ether or hexane until precipitation is complete. Filter and recrystallize from ethanol/water to yield the product 15 g (89%); m.p. 140-142°C.

Anal. Calcd. for C₂₀H₁₈N₃Cl: C, 71.53; H, 5.40; N, 12.51. Found, C, 71.73; H, 5.43; N, 12.27.

B. 8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-
benzo[5,6]cyclohepta[1,2-b]pyridine.

A solution of 14 g of the N-cyano compound from part A in 60 ml of concentrated hydrochloric acid, 600 ml of glacial acetic acid and 400 ml of water is refluxed with stirring for 20 hours. The solvents are removed in vacuo and the residue dissolved in water and neutralized with ammonium hydroxide. The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness and the residue triturated with petroleum ether or hexane yield

-12-

11.5 g (93%) m.p. 149-151°C. After recrystallization from hexane, the product melts at 150-151°C.

Anal. Calcd. for C₁₉H₁₉N₂Cl: C, 73.42; H, 6.16; N, 9.01. Found: C, 73.19; H, 6.14; N, 8.91

The following formulations exemplify some of the dosage forms of the compositions of this invention. In each, the term "active compound" designates the compound, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine or a pharmaceutically acceptable salt, or solvate thereof.

Pharmaceutical Dosage Form Examples

Example A

Tablets

No.	Ingredient	mg/tablet	mg/tablet
1.	Active Compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix item nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with item no. 3. Mill the damp granules through a coarse screen (e.g., 1/4") if needed. Dry the damp granules. Screen the dried

-13-

granules if needed and mix with item no. 4 and mix for 10-15 minutes. Add item no. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

-14-

Example B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active Compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade,	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix item nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add item no. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Example C

Parenteral

Ingredient	mg/vial	mg/vial
Active Compound Sterile Powder	100	500

Add sterile water for injection or bacteriostatic water for injection, for reconstitution.

-15-

Example D

Injectable

<u>Ingredient</u>	<u>mg/vial</u>	<u>mg/vial</u>
Active Compound	100	500
Methylparaben	1.8	1.8
Propylparaben	0.2	0.2
Sodium Bisulfite	3.2	3.2
Disodium Eddetate	0.1	0.1
Sodium Sulfate	2.6	2.6
Water for Injection q.s. ad	1.0 ml	1.0 ml

Method of Manufacture

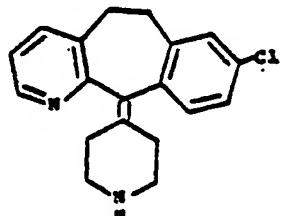
1. Dissolve parabens in a portion (85% of the final volume) of the water for injection at 65-70°C.
2. Cool to 25-35°C. Charge and dissolve the sodium bisulfite, disodium edetate and sodium sulfate.
3. Charge and dissolve drug.
4. Bring the solution to final volume by adding water for injection.
5. Filter the solution through a 0.22 membrane and fill into appropriate containers.
6. Terminally sterilize the units by autoclaving.

The relevant teachings of all published references cited herein are incorporated by reference.

-16-

CLAIMS:

1. The compound 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine having the structural formula:



and the pharmaceutically acceptable salts thereof.

2. The compound defined in claim 1 in the form of the acetic acid salt.

3. Process for the preparation of the compounds defined in claim 1 or 2 characterized in that

- a) 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is decarbethoxylated; or
- b) 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is demethylated

followed by isolation of the compound in the free form or in the form of its salt.

4. A pharmaceutical composition which comprises the compound defined in claim 1 or 2 in combination with a pharmaceutically acceptable carrier.

5. The composition defined in claim 4 in unit dosage form.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/00187

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴ : C 07 D 401/04; A 61 K 31/445

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
IPC ⁴	C 07 D 401/00
<small>Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *</small>	

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. 13
A	US, A, 4282233 (SCHERING CORP.) 4 August 1981 see example 1B; example 4, starting compound (cited in the application) --	1
A	US, A, 3326924 (SCHERING CORP.) 20 June 1967 see column 2, formula III; claims (cited in the application) --	1
A	US, A, 3391143 (SMITH KLINE & FRENCH LABORATORIES) 2 July 1968 see pages 1,2 --	1,3
A	Journal of Medicinal Chemistry, vol. 15, no. 7, 1972 (Columbus, Ohio, US) F.J. Villani et al.: "Derivatives of 10,11-dihydro-5H-dibenzo (a,d)cycloheptene and related compounds. 6. Aminoalkyl derivatives of the aza isosteres", pages 750-	1 ./. .

* Special categories of cited documents: ¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 7th May 1985	Date of Mailing of this International Search Report 13 JUIN 1985
---	---

International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer G.L.M. Kruydenberg
---	---

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	754, see page 751, last paragraph -----	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 8500187 (SA 8975)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/06/85

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US-A- 4282233	04/08/81	EP-A, B JP-A- AU-A- US-A- CA-A- AT-B- AU-B-	0042544 57035586 7186281 4355036 1160230 E9695 543054	30/12/81 26/02/82 24/12/81 19/10/82 10/01/84 15/10/84 28/03/85
US-A- 3326924		NL-A- BE-A- DE-A- DE-A, B, C CH-A- CH-A- CH-A- CH-A- CH-A- DE-A- DE-A- FR-A- FR-M- US-A- US-A- GB-A- US-A- CH-A- NL-C- US-A- SE-B-	6404490 647043 1695853 1470314 533115 535769 538478 542847 544091 1795745 1795744 1406507 4013 3357986 3301863 1065191 3366635 537929 132137 3419565 379765	26/10/64 26/10/64 02/03/72 06/04/72 31/01/73 15/04/73 15/08/73 30/11/73 28/12/73 29/08/74 21/11/74 31/07/73 20/10/75
US-A- 3391143		GB-A-	1165255	24/09/69

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.